Edition: BP 2025 (Ph. Eur. 11.6 update)

Timolol Eye Drops

General Notices

Action and use

Beta-adrenoceptor antagonist; treatment of glaucoma.

DEFINITION

Timolol Eye Drops are a sterile solution of Timolol Maleate in Purified Water.

The eye drops comply with the requirements stated under Eye Preparations and with the following requirements.

Content of timolol, $C_{13}H_{24}N_4O_3S$

90.0 to 110.0% of the stated amount.

IDENTIFICATION

A. Add a volume of the eye drops containing the equivalent of 50 mg of timolol to an equal volume of *carbonate buffer pH 9.7* and extract with two 40-mL quantities of *dichloromethane*. Reserve the aqueous layer for test B, dry the extracts with *anhydrous sodium sulfate*, evaporate to dryness using a rotary evaporator and dry at 60° under reduced pressure for 15 minutes. The *infrared absorption spectrum* of the residue, Appendix II A, is concordant with the *reference spectrum* of timolol (*RS 339*).
B. Evaporate the aqueous solution reserved in test A to about 1 mL. Add 1 mL of *bromine solution*, heat in a water bath for 10 minutes, boil, cool and add 0.1 mL of the solution to a solution of 10 mg of *resorcinol* in 3 mL of *sulfuric acid*. A bluish black colour is produced on heating in a water bath for 15 minutes.

TESTS

Acidity or alkalinity

pH, 6.5 to 7.5, Appendix V L.

Related substances

Carry out the method for *liquid chromatography*, Appendix III D, using the following solutions.

(1) Use the eye drops undiluted.
(2) Dilute 1 volume of the eye drops to 250 volumes with the mobile phase.
(3) Dilute 1 volume of the eye drops to 500 volumes with the mobile phase.
(4) 0.30% w/v of *maleic acid* in the mobile phase.

CHROMATOGRAPHIC CONDITIONS

(a) Use a stainless steel column (25 cm × 4 mm) packed with *end-capped octadecylsilyl silica gel for chromatography* (10 µm) (Nucleosil C18 is suitable).
(b) Use isocratic elution and the mobile phase described below.
(c) Use a flow rate of 2 mL per minute.
(d) Use an ambient column temperature.
(e) Use a detection wavelength of 295 nm.
(f) Inject 20 µL of each solution.
(g) Allow the chromatography to proceed for 4 times the retention time of the principal peak.

MOBILE PHASE

42.5 volumes of 0.02M *sodium octanesulfonate* and 57.5 volumes of *methanol*, adjusted to pH 3.0 using *glacial acetic acid*.

LIMITS

In the chromatogram obtained with solution (1):

the area of any *secondary peak*, other than the peak corresponding to maleic acid, is not greater than the area of the peak obtained with solution (2) (0.4%);

not more than two such peaks have an area greater than that of the peak obtained with solution (3) (0.2%).

ASSAY

Dilute a volume containing the equivalent of 25 mg of timolol to 50 mL with *water*. To 5 mL add 15 mL of *carbonate buffer pH 9.7* and extract with three 20-mL quantities and one 10-mL quantity of *toluene*. Wash each extract successively with the same 10 mL volume of *carbonate buffer pH 9.7*, combine the toluene extracts and extract with four 20-mL quantities of 0.05M *sulfuric acid*. Combine the extracts, dilute to 100 mL, filter and measure the *absorbance* at the maximum at 295 nm, Appendix II B, using in the reference cell a solution prepared by treating 5 mL of *water* in the same manner, beginning at the words ‘add 15 mL...’. Calculate the content of $C_{13}H_{24}N_4O_3S$ taking 279 as the value of A(1%, 1 cm) at the maximum at 295 nm.

LABELLING

The quantity of active ingredient is stated in terms of the equivalent amount of timolol.